Observational Study

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Correlations between the properties of saliva and metabolic syndrome

A prospective observational study

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Abstract

Saliva tests, which are easy to perform and non-invasive, can be used to monitor both oral disease (especially periodontal disease) and physical conditions, including metabolic syndrome (MetS). Therefore, in the present study the associations between saliva test results and MetS were investigated based on medical health check-up data for a large population. In total, 1,888 and 2,296 individuals underwent medical check-ups for MetS and simultaneous saliva tests in 2017 and 2018, respectively. In the saliva tests, the buffer capacity of saliva, salivary pH, the salivary white blood cell count, the number of cariogenic bacteria in saliva, salivary occult blood, protein, and ammonia levels were tested using a commercially available kit. The relationships between the results of the saliva tests and MetS components were examined in cross-sectional and longitudinal multivariate analyses. Significant relationships were detected between salivary protein levels and serum HbA1c levels or blood pressure levels and between the buffer capacity of saliva and serum triglyceride levels. In addition, salivary pH was increased irreversibly by impaired renal function. This study suggested that saliva tests conducted during health check-ups of large populations might be a useful screening tool for periodontal disease and MetS/MetS components.

Abbreviations: CKD = chronic kidney disease, DM = diabetes mellitus, HDL-C = high-density lipoprotein cholesterol, MetS = metabolic syndrome, SMT = salivary Multi Test, WBC = white blood cell.

Keywords: saliva test, metabolic syndrome, medical check-up, blood pressure, screening, periodontal disease

1. Introduction

Metabolic syndrome (MetS) is a complex medical disorder, which is defined as the presence of three out of five interrelated conditions attributed to visceral fat-type obesity, including hypertension and abnormal glucose and lipid metabolism.[1,2] MetS was reported to increase the risk of cardiovascular disease, including atherosclerotic cardiovascular disease, and type 2 diabetes mellitus (DM).[3,4] The prevalence of MetS has increased worldwide.[5] In 2011–2012, the estimated prevalence of MetS in the USA was 34.7% and increased with age; that is, it was 18.3% in adults aged 20 to 39 years and 46.7% in those aged ≥60 years.[6] In middle-aged Japanese individuals, the prevalence of MetS was reported to be 14.9%.[7]

Periodontitis is a pathological infectious inflammatory disease, which causes the destruction of periodontal tissue and can lead to tooth loss [8]. In previous studies,[7,9–11] a close correlation was detected between periodontitis and MetS, and individuals with MetS have been reported to present with a worse periodontal status, including a higher prevalence of periodontitis, more severe periodontitis, and more wide-ranging periodontitis.[10] Many chronic diseases, including periodontitis, hypertension, and DM, are influenced by common risk factors including diet, smoking, alcohol, a lack of exercise, and stress.[12,13] It has been reported that chronic systemic inflammation might predispose individuals with periodontal disease to develop components of MetS or vice versa.[14] Therefore, investigations and health public policies targeting MetS and periodontitis are important for promoting public health.

Saliva tests are easy to conduct and non-invasive, and it has been reported that such tests can produce clinically significant information relating to both systemic and oral disease.[15–21] Many researchers have reported that saliva-based screening tests are useful for diagnosing periodontitis.[15–21] As stated above,

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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periodontitis and MetS are closely related and influenced by the same common risk factors[22]. Previously, we reported the effectiveness of incorporating dental check-ups into health check-ups and detected a significant association between periodontitis and MetS.[11] These results suggested that saliva tests could be used to monitor not only periodontal conditions, but also physical conditions related to MetS. Therefore, the purpose of the present study was to investigate the associations between the results of saliva tests and MetS based on medical health check-up data for a large population.

2. Materials and methods

The protocol of the present study was approved by the Committee on Medical Research of Shinshu University (♯2775). Individuals who underwent specific health check-ups (health check-ups for MetS) in the Japanese cities Azumino and Shiojiri between 2017 and 2018 were invited to participate in the study. All of the subjects, which included self-employed workers, farmers, and the elderly, were insured by the Japanese national health insurance system and were aged ≥25 years. They all provided written informed consent before participating in this study. The subjects underwent saliva tests during their health check-ups. The health check-ups were conducted according to the standard program provided by the Ministry of Health, Labour and Welfare of Japan (2013).[23] They included an interview on lifestyle and systemic disease treatment status (including on recent smoking habits and whether the patient was taking medication for hypertension, lipid abnormalities, or hyperglycemia); height, weight, abdominal circumference, and blood pressure measurements; and blood tests (of triglyceride, high-density lipoprotein cholesterol [HDL-C], blood sugar, hemoglobin A1c [HbA1c], and creatinine levels).

Regarding the saliva tests, each saliva sample was collected with 3 ml of mouthwash and was immediately evaluated using a commercially available test kit (Salivary Multi Test [SMT]; LION Dental Products Co., Ltd., Tokyo, Japan). The saliva tests were performed according to the manufacturer's protocols and were used to evaluate the buffer capacity of saliva; the number of cariogenic bacteria present in saliva; salivary pH; salivary occult blood, protein, and ammonia levels; and the salivary white blood cell (WBC) count. The test kit consisted of test strips and a measuring device. In this test, the color changes that occur in each pad of the test strip are assessed by measuring reflectance at a specific wavelength. Specifically, the number of cariogenic bacteria present in saliva is evaluated based on the reduction of resazurin sodium by Gram-positive bacteria. The salivary pH is assessed based on the color change exhibited by a pH indicator. The buffer capacity is determined based on the color change exhibited a compound pH indicator in the presence of a fixed quantity of acid. The salivary occult blood level is assessed by measuring pseudo-peroxidase activity in hemoglobin. The WBC count is evaluated by measuring leukocyte esterase activity, the salivary protein level is determined based on the "protein error of indicators" phenomenon. The salivary ammonia level is assessed based the color change seen after the addition of bromocresol green. The principles underlying the measurement of each parameter are summarized in Figure 1. The results of the saliva tests are expressed as percentages (0–100) and were classified into three categories (high, moderate, and low), according to the values established by the manufacturer.[24] Individuals who had been eating/drinking, had brushed their teeth, or had gargled within 2 two hours before the salivary test were excluded from the study because these might have affected the test results. The dental examination also included assessments of dental and periodontal conditions by well-trained dentists. The grade of

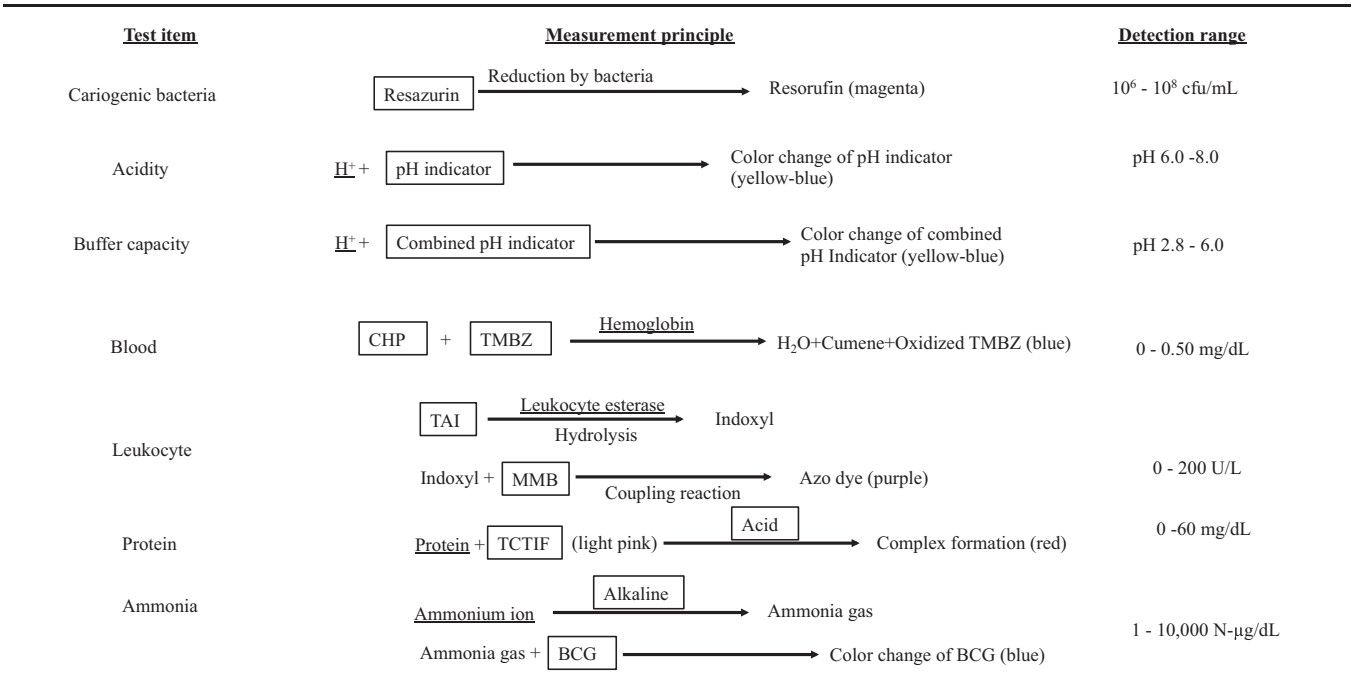

Figure 1. Detection principle of the Salivary Multi Test. _: Detected substance □: Ingredient in test strip. CHP: cumene hydroperoxide, TMBZ: 3,3',5,5'-tetramethylbenzidine, TAI: 3-(*N*-toluenesulfonyl-L-alanyloxy)indole, MMB: 2-methoxy-4-(*N*-morpholino)benzenediazonium, TCTIF: 4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein disodium salt, BCG: bromocresol green, cfu: colony forming unit.

periodontal disease was assessed according to the World Health Organization (WHO) Community Periodontal Index (CPI) criteria.[25] PD was measured using standard WHO probes. Periodontal disease was diagnosed according to the CPI code: Code 0 (healthy periodontal condition) was judged as healthy, Codes 1 and 2 (with gingival bleeding on probing, BOP) as gingivitis, and Codes 3 and 4 (PD ≥ 4 mm) as periodontitis.

The results of the saliva test were compared with the results of the health check-up in the cross-sectional analysis. In addition, in the longitudinal analysis the relationships between the changes in the saliva test results and the changes in the health check-up results were analyzed in the individuals who underwent examinations in both 2017 and 2018. In this study, the interyear changes in the saliva test results that occurred between 2017 and 2018 were classified into the four following categories:

Remained high: "high" in both 2017 and 2018
Increased: "moderate/low" in 2017 and "high" in 2018
Decreased: "high" in 2017 and "moderate/low" in 2018
Remained low: "moderate/low" in both 2017 and 2018

Statistical analyses were performed using JMP ver.13 (SAS Institute Inc., NC). In the cross-sectional analysis, the correlations between the results of the saliva test and the health check-up results were examined using univariate analyses (Spearman's rank correlation coefficient) and multivariate analysis involving common risk (confounding) factors. In the longitudinal analysis, the correlations between the interyear changes in the results of the saliva test and the interyear changes in the health check-up parameters (the value obtained in 2018 minus the value obtained in 2017) were evaluated using univariate analyses (involving the Tukey-Kramer HSD test) and multivariate analysis of common risk factors (sex, age in 2017, change in BMI, and change in smoking habits). P values of $<.05$ were considered to indicate statistical significance.

3. Results

Among the individuals who underwent the health check-up, 1,887 (24.0%) out of the 7,848 individuals who underwent the health check-up in 2017 and 2,279 (32.2%) out of the 7,084 individuals who underwent the health check-up in 2018 consented to saliva tests and participated in the study. The subjects' characteristics and the results of the saliva tests are summarized in Table 1.

3.1. The results of the cross-sectional analysis

The correlations between systolic or diastolic blood pressure and the results of the saliva test are shown in Tables 2 and 3. This analysis included the data from the subjects who were not taking antihypertensive medication (n = 1,374). Although in the univariate analyses weak but significant correlations were observed between systolic or diastolic blood pressure and the buffer capacity of saliva (diastolic blood pressure: $P<.05$) or the salivary levels of occult blood (systolic blood pressure: $P<.05$; diastolic blood pressure: $P<.05$), protein (systolic blood pressure; $P<.01$; diastolic blood pressure: $P<.05$), or ammonia (systolic blood pressure: $P<.01$; diastolic blood pressure: $P<.01$), the multivariate analysis did not reveal any significant correlations between these parameters. The only significant correlation found in the multivariate analysis was between systolic blood pressure and the number of cariogenic bacteria in saliva ($P<.05$), even though no such correlation was detected in the univariate analysis.

Table 1

Characteristics of studied subjects.

	2017 Number (%)	2018 Number (%)
Number of subjects received the specific health check-ups	7,848	7,084
Number of subjects received salivary examination	1, 887 (24.0)	2,279 (32.2)
Gender		
Male	875 (46.3)	1,119 (49.1)
Female	1, 012 (53.7)	1,160 (50.9)
Age		
Average ± SD	64.8 ± 12.9	67.6 ± 11.7
Range	25-95	29-96
Results of the salivary examination using SMT	1,887	2,279
Cariologenic bacteria		
Much	994 (52.7%)	1,051 (46.1%)
Average	495 (26.2%)	542 (23.8%)
Little	399 (21.1%)	686 (30.1%)
Acidity		
Much	1,239 (65.3%)	1,571 (69.9%)
Average	430 (22.8%)	485 (21.3%)
Little	219 (11.6%)	223 (9.8%)
Buffer capacity		
Much	757 (40.1%)	921 (40.4%)
Average	640 (33.9%)	788 (34.6%)
Little	491 (26.0%)	570 (25.0%)
Occult blood		
Much	941 (49.9)	1,253 (55.0)
Average	596 (31.6)	693 (30.4)
Little	350 (18.5)	333 (14.6)
White blood cell		
Much	1,050 (55.6)	1,253 (55.0)
Average	546 (28.9)	708 (31.1)
Little	291 (15.4)	318 (14.0)
Protein		
Much	1,253 (66.4)	1,463 (64.2)
Average	395 (20.9)	528 (23.2)
Little	239 (12.7)	288 (12.6)
Ammonium		
Much	1,541 (81.7)	1,858 (81.5)
Average	253 (13.4)	312 (13.7)
Little	93 (4.9)	109 (4.8)

SD: standard diviation.

The correlations between serum triglyceride or HDL-C levels and the results of the saliva test are shown in Tables 4 and 5. This analysis included the data for the subjects who were not taking antihyperlipidemic medication (n = 1,545). The weak but significant or nearly significant correlations were observed between serum triglyceride or HDL-C levels and salivary buffer capacity (serum HDL-C level: $P<.05$), the salivary levels of occult blood (serum triglyceride level: $P<.05$; serum HDL-C level: $P<.01$) or protein (serum triglyceride level: $P<.01$; serum HDL-C level: $P<.01$), or the salivary WBC count (serum triglyceride level: $P<.05$; serum HDL-C level: $P=0.058$) in the univariate analyses However, the multivariate analysis only showed nearly significant correlations between the serum triglyceride ($P=.053$) or HDL-C ($P=.091$) level and the salivary WBC count. In addition, the multivariate analysis revealed significant correlations between the serum triglyceride level and salivary buffer capacity ($P<.05$) and between the serum HDL-C level and salivary pH ($P<.05$) or the salivary ammonia level ($P<.01$); however, no significant correlations were observed between these parameters in the univariate analyses.

Table 2

Correlation between systolic blood pressure and results of salivary multi test in those who had no antihypertensive medication (n = 1,374).

			Univariate analysis						Multivariate analysis				
			Systolic blood pressure				Spearman's rank correlation						
	Level	n	Average	SE	95%CI		r	*P* value		Estimate	SE	*t* value	*P* value
Cariogenic bacteria	Much	703	122.0	0.62	120.8	123.2	−0.005	.853	Cariogenic bacteria	−1.041	0.506	−2.06	<.05
	Average	362	122.2	0.86	120.5	123.9			Sex (woman/man)	−0.465	0.432	−1.08	.283
	Little	309	122.6	0.93	120.8	124.4			Age (years)	0.379	0.031	12.17	<.01
									BMI (kg/m2)	1.246	0.130	9.55	<.01
									Smoking (no/yes)	−0.893	0.747	−1.2	.232
Acidity	Much	912	121.9	0.5	120.9	123.0	−0.026	.342	Acidity	0.182	0.603	0.3	.763
	Average	310	122.6	0.9	120.7	124.4			Sex (woman/man)	−0.485	0.436	−1.11	.266
	Little	152	123.1	1.3	120.5	125.7			Age (years)	0.372	0.031	11.98	<.01
									BMI (kg/m2)	1.240	0.131	9.5	<.01
									Smoking (no/yes)	−0.855	0.752	−1.14	.256
Buffer capacity	Much	508	123.5	0.7	122.1	125.0	−0.026	.342	Buffer capacity	−0.606	0.541	−1.12	.263
	Average	471	122.6	0.8	121.1	124.1			Sex (woman/man)	−0.550	0.439	−1.25	.211
	Little	395	120.0	0.8	118.4	121.6			Age (years)	0.383	0.033	11.75	<.01
									BMI (kg/m2)	1.244	0.131	9.52	<.01
									Smoking (no/yes)	−0.835	0.749	−1.12	.265
Occult Blood	Much	638	123.5	0.6	122.2	124.8	0.117	<.01	Occult Blood	0.071	0.544	0.13	.897
	Average	460	122.1	0.8	120.6	123.6			Sex (woman/man)	−0.469	0.433	−1.08	.280
	Little	276	119.4	1.0	117.5	121.3			Age (years)	0.370	0.032	11.67	<.01
									BMI (kg/m2)	1.239	0.131	9.45	<.01
									Smoking (no/yes)	−0.871	0.750	−1.16	.246
Protein	Much	854	123.4	0.6	122.3	124.5	0.111	<.01	Protein	−0.306	0.593	−0.52	.606
	Average	321	121.2	0.9	119.4	122.9			Sex (woman/man)	−0.473	0.433	−1.09	.275
	Little	199	118.6	1.2	116.4	120.9			Age (years)	0.377	0.033	11.45	<.01
									BMI (kg/m2)	1.245	0.131	9.51	<.01
									Smoking (no/yes)	−0.868	0.748	−1.16	.246
Leukocyte	Much	734	122.5	0.6	121.3	123.7	0.031	.252	Leukocyte	−0.435	0.549	−0.79	.428
	Average	411	122.3	0.8	120.7	123.9			Sex (woman/man)	−0.453	0.434	−1.05	.296
	Little	229	121.0	1.1	118.9	123.1			Age (years)	0.375	0.031	11.97	<.01
									BMI (kg/m2)	1.243	0.131	9.51	<.01
									Smoking (no/yes)	−0.885	0.748	−1.18	.237
Ammonia	Much	1088	123.1	0.5	122.1	124.0	0.111	<.01	Ammonia	0.598	0.770	0.78	.438
	Average	209	119.9	1.1	117.7	122.1			Sex (woman/man)	−0.442	0.435	−1.02	.309
	Little	77	116.2	1.9	112.6	119.8			Age (years)	0.364	0.032	11.31	<.01
									BMI (kg/m2)	1.239	0.131	9.48	<.01
									Smoking (no/yes)	−0.896	0.748	−1.2	.231

SE: standard error, CI: confidence interval.

Table 3

Correlation between diastolic blood pressure and results of salivary multi test in those who had no antihypertensive medication (n = 1,374).

			Univariate analysis						Multivariate analysis				
			Diastolic blood pressure				Spearman's rank correlation						
	Level	n	Average	SE	95%CI		r	*P* value		Estimate	SE	*t* value	*P* value
Cariogenic bacteria	Much	703	73.9	0.41	73.1	74.7	−0.004	.880	Cariogenic bacteria	−0.529	0.340	−1.56	.120
	Average	362	74.1	0.57	73.0	75.3			Sex (woman/man)	−1.726	0.290	−5.94	<.01
	Little	309	74.3	0.62	73.1	75.5			Age (years)	0.154	0.021	7.36	<.01
									BMI (kg/m2)	0.798	0.088	9.11	<.01
									Smoking (no/yes)	−0.908	0.502	−1.81	.071
Acidity	Much	912	73.9	0.36	73.2	74.6	−0.024	.380	Acidity	0.119	0.405	0.29	.769
	Average	310	74.2	0.62	73.0	75.4			Sex (woman/man)	−1.739	0.293	−5.94	<.01
	Little	152	74.8	0.88	73.0	76.5			Age (years)	0.151	0.021	7.23	<.01
									BMI (kg/m2)	0.795	0.088	9.07	<.01
									Smoking (no/yes)	−0.885	0.504	−1.76	.080
Buffer capacity	Much	508	74.8	0.48	73.8	75.7	0.06	<.05	Buffer capacity	−0.377	0.363	−1.04	.299
	Average	471	74.3	0.50	73.3	75.2			Sex (woman/man)	−1.778	0.295	−6.04	<.01
	Little	395	72.9	0.55	71.8	74.0			Age (years)	0.157	0.022	7.19	<.01
									BMI (kg/m2)	0.797	0.088	9.1	<.01
									Smoking (no/yes)	−0.873	0.502	−1.74	.082
Occult Blood	Much	638	74.6	0.43	73.7	75.4	0.065	<.05	Occult Blood	−0.048	0.365	−0.13	.895

(*continued*)

Table 3

(continued).

			Univariate analysis						Multivariate analysis				
			Diastolic blood pressure				Spearman's rank correlation						
	Level	n	Average	SE	95%CI		r	*P* value		Estimate	SE	*t* value	*P* value
	Average	460	74.4	0.51	73.4	– 75.4			Sex (woman/man)	−1.729	0.291	−5.95	<.01
	Little	276	72.4	0.65	71.1	– 73.7			Age (years)	0.151	0.021	7.07	<.01
						–			BMI (kg/m2)	0.796	0.088	9.05	<.01
						–			Smoking (no/yes)	−0.904	0.503	−1.8	.073
Protein	Much	854	74.5	0.37	73.8	– 75.2	0.069	<.05	Protein	−0.221	0.398	−0.56	.578
	Average	321	74.0	0.61	72.8	– 75.2			Sex (woman/man)	−1.731	0.291	−5.96	<.01
	Little	199	72.3	0.77	70.8	– 73.8			Age (years)	0.154	0.022	6.98	<.01
						–			BMI (kg/m2)	0.798	0.088	9.09	<.01
						–			Smoking (no/yes)	−0.893	0.502	−1.78	.076
Leukocyte	Much	734	74.4	0.40	73.6	– 75.1	0.044	.106	Leukocyte	0.269	0.369	0.73	.465
	Average	411	74.1	0.54	73.1	– 75.2			Sex (woman/man)	−1.738	0.291	−5.97	<.01
	Little	229	73.0	0.72	71.5	– 74.4			Age (years)	0.148	0.021	7.01	<.01
						–			BMI (kg/m2)	0.794	0.088	9.06	<.01
						–			Smoking (no/yes)	−0.895	0.502	−1.78	.075
Ammonia	Much	1088	74.5	0.33	73.9	– 75.2	0.086	<.01	Ammonia	0.553	0.517	1.07	.2845
	Average	209	72.9	0.75	71.4	– 74.3			Sex (woman/man)	−1.703	0.292	−5.84	<.01
	Little	77	70.5	1.23	68.1	– 72.9			Age (years)	0.144	0.022	6.65	<.01
									BMI (kg/m2)	0.793	0.088	9.05	<.01
									Smoking (no/yes)	−0.917	0.502	−1.83	.068

SE: standard error CI: confidence interval.

Table 4

Correlation between triglyceride and results of salivary multi test in those who had no antihyperlipidemic medication (n = 1,545).

			Univariate analysis						Multivariate analysis				
			Triglyceride				Spearman's rank correlation						
	Level	n	Average	SE	95%CI		r	*P* value		Estimate	SE	*t* value	*P* value
Cariogenic bacteria	Much	797	110.3	2.51	105.4	– 115.2	−0.011	.680	Cariogenic bacteria	−4.037	2.123	−1.9	.058
	Average	414	116.0	3.48	109.2	– 122.9			Sex (woman/man)	−6.484	1.788	−3.63	<.01
	Little	334	114.6	3.88	107.0	– 122.2			Age (years)	0.453	0.131	3.47	<.01
						–			BMI (kg/m2)	6.359	0.533	11.92	<.01
						–			Smoking (no/yes)	−10.438	3.078	−3.39	<.01
Acidity	Much	1033	113.9	2.21	109.6	– 118.3	0.01	.696	Acidity	3.945	2.480	1.59	.112
	Average	336	110.9	3.87	103.4	– 118.5			Sex (woman/man)	−6.782	1.799	−3.77	<.01
	Little	176	109.3	5.35	98.8	– 119.8			Age (years)	0.437	0.130	3.36	<.01
						–			BMI (kg/m2)	6.332	0.534	11.87	<.01
						–			Smoking (no/yes)	−9.965	3.091	−3.22	.001
Buffer capacity	Much	596	113.3	2.91	107.6	– 119.0	0.016	.527	Buffer capacity	−5.276	2.247	−2.35	<.05
	Average	517	111.8	3.12	105.7	– 117.9			Sex (woman/man)	−7.226	1.816	−3.98	<.01
	Little	432	113.2	3.41	106.5	– 119.9			Age (years)	0.525	0.137	3.84	<.01
						–			BMI (kg/m2)	6.335	0.533	11.89	<.01
						–			Smoking (no/yes)	−10.233	3.077	−3.33	<.01
Occult Blood	Much	755	117.5	2.57	112.5	– 122.5	0.087	<.01	Occult Blood	2.817	2.263	1.24	.213
	Average	488	113.1	3.20	106.8	– 119.4			Sex (woman/man)	−6.395	1.791	−3.57	<.01
	Little	302	100.4	4.07	92.4	– 108.4			Age (years)	0.385	0.133	2.89	<.01
						–			BMI (kg/m2)	6.286	0.536	11.74	<.01
						–			Smoking (no/yes)	−10.157	3.086	−3.29	<.01
Protein	Much	992	116.8	2.25	112.4	– 121.2	0.083	<.01	Protein	4.173	2.472	1.69	.092
	Average	334	107.8	3.87	100.3	– 115.4			Sex (woman/man)	−6.367	1.790	−3.56	<.01
	Little	219	102.2	4.78	92.8	– 111.5			Age (years)	0.344	0.138	2.5	<.05
						–			BMI (kg/m2)	6.317	0.534	11.84	<.01
						–			Smoking (no/yes)	−10.403	3.079	−3.38	<.01
Leukocyte	Much	842	116.1	2.44	111.3	– 120.9	0.054	<.05	Leukocyte	4.409	2.281	1.93	.0534
	Average	449	111.4	3.34	104.8	– 117.9			Sex (woman/man)	−6.560	1.789	−3.67	<.01
	Little	254	104.1	4.44	95.4	– 112.9			Age (years)	0.382	0.131	2.91	<.01
						–			BMI (kg/m2)	6.318	0.533	11.84	<.01
						–			Smoking (no/yes)	−10.386	3.078	−3.37	<.01
Ammonia	Much	1235	113.9	2.02	110.0	– 117.9	0.036	.156	Ammonia	0.585	3.241	0.18	.8569
	Average	226	111.0	4.71	101.8	– 120.3			Sex (woman/man)	−6.452	1.796	−3.59	<.01
	Little	84	100.1	7.73	84.9	– 115.2			Age (years)	0.417	0.135	3.09	<.01
						–			BMI (kg/m2)	6.340	0.534	11.87	<.01
									Smoking (no/yes)	−10.402	3.083	−3.37	<.01

SE: standard error CI: confidence interval.

Table 5

Correlation between HDL-cholesterol and results of salivary multi test in those who had no antihyperlipidemic medication (n = 1,545).

			Univariate analysis							Multivariate analysis				
			HDL-cholesterol					Spearman's rank correlation						
	Level	n	Average	SE	95%CI			r	*P* value		Estimate	SE	*t* value	*P* value
Cariogenic bacteria	Much	797	63.6	0.58	62.4	–	64.7	−0.014	.580	Cariogenic bacteria	0.174	0.460	0.38	.706
	Average	414	63.8	0.80	62.2	–	65.4			Sex (woman/man)	4.260	0.387	11	<.01
	Little	334	63.8	0.89	62.1	–	65.6			Age (years)	−0.057	0.028	−2.03	<.05
						–				BMI (kg/m2)	−1.577	0.115	−13.66	<.01
						–				Smoking (no/yes)	0.912	0.666	1.37	.171
Acidity	Much	1033	63.5	0.51	62.5	–	64.5	−0.009	.723	Acidity	−1.096	0.536	−2.04	<.05
	Average	336	64.2	0.89	62.5	–	66.0			Sex (woman/man)	4.344	0.389	11.17	<.01
	Little	176	63.9	1.22	61.5	–	66.3			Age (years)	−0.060	0.028	−2.13	<.05
						–				BMI (kg/m2)	−1.574	0.115	−13.65	<.01
						–				Smoking (no/yes)	0.792	0.668	1.19	.236
Buffer capacity	Much	596	62.7	0.66	61.4	–	64.0	−0.062	<.05	Buffer capacity	0.563	0.487	1.16	.247
	Average	517	63.8	0.71	62.4	–	65.2			Sex (woman/man)	4.339	0.393	11.04	<.01
	Little	432	64.8	0.78	63.3	–	66.4			Age (years)	−0.067	0.030	−2.26	<.05
						–				BMI (kg/m2)	−1.576	0.115	−13.66	<.01
						–				Smoking (no/yes)	0.893	0.666	1.34	.180
Occult Blood	Much	755	62.2	0.59	61.1	–	63.4	−0.107	<.01	Occult Blood	−0.785	0.489	−1.61	.109
	Average	488	64.3	0.73	62.8	–	65.7			Sex (woman/man)	4.236	0.387	10.94	<.01
	Little	302	66.4	0.93	64.6	–	68.3			Age (years)	−0.045	0.029	−1.58	.115
						–				BMI (kg/m2)	−1.561	0.116	−13.49	<.01
						–				Smoking (no/yes)	0.845	0.667	1.27	.205
Protein	Much	992	62.7	0.51	61.7	–	63.7	−0.082	<.01	Protein	−0.711	0.535	−1.33	.184
	Average	334	65.4	0.89	63.7	–	67.2			Sex (woman/man)	4.240	0.387	10.95	<.01
	Little	219	65.3	1.09	63.2	–	67.5			Age (years)	−0.043	0.030	−1.43	.153
						–				BMI (kg/m2)	−1.573	0.115	−13.62	<.01
						–				Smoking (no/yes)	0.912	0.666	1.37	.171
Leukocyte	Much	842	63.1	0.56	62.0	–	64.2	−0.048	.058	Leukocyte	−0.834	0.493	−1.69	.091
	Average	449	63.9	0.77	62.4	–	65.4			Sex (woman/man)	4.275	0.387	11.05	<.01
	Little	254	65.3	1.02	63.3	–	67.2			Age (years)	−0.048	0.028	−1.7	.089
						–				BMI (kg/m2)	−1.572	0.115	−13.63	<.01
						–				Smoking (no/yes)	0.909	0.666	1.37	.172
Ammonia	Much	1235	63.8	0.46	62.9	–	64.7	0.008	.766	Ammonia	1.984	0.699	2.84	<.01
	Average	226	63.6	1.08	61.4	–	65.7			Sex (woman/man)	4.347	0.387	11.22	<.01
	Little	84	62.8	1.77	59.3	–	66.3			Age (years)	−0.079	0.029	−2.71	<.01
						–				BMI (kg/m2)	−1.581	0.115	−13.73	<.01
										Smoking (no/yes)	0.868	0.665	1.31	.192

SE: standard error CI: confidence interval.

The correlations between the serum HbA1C level and the results of the saliva test are shown in Table 6. This analysis included the data for the subjects who were not taking antidiabetic medication (n = 1,769). A significant correlation was found between the serum HbA1C level and salivary buffer capacity in both the univariate and multivariate analyses (univariate analysis: $P < .01$; multivariate analysis: $P < .05$). In addition, a significant correlation between the serum HbA1C level and the salivary protein level was detected in the univariate analyses, and a nearly significant correlation between these parameters was found in the multivariate analysis ($P = .060$). While the serum HbA1C level exhibited significant correlations with the salivary occult blood level, WBC count, and ammonia level in the univariate analyses, no such correlations were found in the multivariate analysis.

The correlations between the serum creatinine level and the results of the saliva test are shown in Table 7. Significant correlations were found between the serum creatinine level and salivary pH or buffer capacity in both the univariate and multivariate analyses (pH: univariate analysis, $P < .01$, multivariate analysis, $P < .01$; buffer capacity: univariate analysis, $P < .01$, and multivariate analysis, $P < .01$). Although weak but significant correlations were observed between the serum creatinine level and the number of cariogenic bacteria in saliva ($P < .05$), the salivary occult blood level ($P < .01$), the salivary protein level ($P < .01$), and the salivary ammonia level ($P < .01$) in the univariate analyses, no such correlations between these parameters were detected in the multivariate analysis.

3.2. The results of the longitudinal analysis

The correlations between the interyear changes in systolic and diastolic blood pressure and the interyear changes in the saliva test results are shown in Tables 8 and 9. This analysis included the data for the subjects who were not taking antihypertensive medication in either 2017 or 2018 (n = 539). The interyear change in systolic blood pressure was significantly correlated with the interyear changes in the salivary protein level ($P < .01$) and WBC count ($P < .01$), whereas diastolic blood pressure was significantly correlated with the interyear change in the salivary protein level ($P < .01$). The subjects that exhibited high salivary protein levels and WBC counts in both 2017 and 2018 had elevated blood pressure, while those with low salivary protein levels and WBC counts displayed decreased blood pressure in both years.

Table 6

Correlation between HbA1c and results of salivary multi test in those who had no antidiabetic medication (n = 1,769).

			Univariate analysis						Multivariate analysis				
			HbA1c				Spearman's rank correlation						
	Level	n	Average	SE	95%CI		r	*P* value		Estimate	SE	*t* value	*P* value
Cariogenic bacteria	Much	926	5.72	0.02	5.69	– 5.75	0.017	.483	Cariogenic bacteria	0.000	0.001	0.13	.895
	Average	467	5.71	0.02	5.67	– 5.75			Sex (woman/man)	0.024	0.015	1.63	.103
	Little	376	5.71	0.02	5.66	– 5.76			Age (years)	0.011	0.001	9.73	<.01
						–			BMI (kg/m2)	0.033	0.004	7.61	<.01
						–			Smoking (no/yes)	−0.019	0.026	−0.71	.475
Acidity	Much	1156	5.72	0.01	5.69	– 5.74	−0.018	.451	Acidity	0.021	0.015	1.38	.168
	Average	405	5.72	0.02	5.67	– 5.76			Sex (woman/man)	0.023	0.011	2.03	<.05
	Little	208	5.69	0.03	5.63	– 5.76			Age (years)	0.010	0.001	11.39	<.01
						–			BMI (kg/m2)	0.027	0.003	8.24	<.01
						–			Smoking (no/yes)	0.003	0.021	0.17	.869
Buffer capacity	Much	697	5.75	0.02	5.72	– 5.79	0.129	<.01	Buffer capacity	0.026	0.011	2.29	<.05
	Average	603	5.73	0.02	5.69	– 5.77			Sex (woman/man)	0.009	0.001	10.54	<.01
	Little	469	5.63	0.02	5.59	– 5.68			Age (years)	0.027	0.003	8.26	<.01
						–			BMI (kg/m2)	0.001	0.020	0.03	.974
						–			Smoking (no/yes)	0.009	0.014	0.64	.522
Occult Blood	Much	870	5.74	0.02	5.71	– 5.77	0.079	<.01	Occult Blood	0.004	0.014	0.31	.758
	Average	562	5.72	0.02	5.68	– 5.76			Sex (woman/man)	0.025	0.011	2.22	<.05
	Little	337	5.63	0.03	5.58	– 5.68			Age (years)	0.009	0.001	10.95	<.01
						–			BMI (kg/m2)	0.027	0.003	8.21	<.01
						–			Smoking (no/yes)	0.001	0.020	0.07	.943
Protein	Much	1427	5.74	0.01	5.71	– 5.76	0.157	<.01	Protein	0.030	0.016	1.88	.060
	Average	249	5.66	0.03	5.60	– 5.72			Sex (woman/man)	0.025	0.011	2.25	<.05
	Little	93	5.51	0.05	5.42	– 5.61			Age (years)	0.009	0.001	10.02	<.01
						–			BMI (kg/m2)	0.027	0.003	8.2	<.01
						–			Smoking (no/yes)	0.001	0.020	0.05	.963
Leukocyte	Much	980	5.74	0.02	5.71	– 5.77	0.061	<.05	Leukocyte	0.014	0.015	0.96	.339
	Average	512	5.70	0.02	5.66	– 5.74			Sex (woman/man)	0.024	0.011	2.17	<.05
	Little	277	5.65	0.03	5.59	– 5.71			Age (years)	0.009	0.001	11.01	<.01
						–			BMI (kg/m2)	0.027	0.003	8.26	<.01
						–			Smoking (no/yes)	0.001	0.020	0.06	.955
Ammonia	Much	1427	5.74	0.01	5.71	– 5.76	0.135	<.01	Ammonia	0.034	0.021	1.65	.098
	Average	249	5.66	0.03	5.60	– 5.72			Sex (woman/man)	0.026	0.011	2.33	<.05
	Little	93	5.51	0.05	5.42	– 5.61			Age (years)	0.009	0.001	10.47	<.01
						–			BMI (kg/m2)	0.027	0.003	8.23	<.01
									Smoking (no/yes)	0.001	0.020	0.03	.980

SE: standard error, CI: confidence interval.

Table 7

Correlation between serum creatinine and results of salivary multi test (n = 1,888).

			Univariate analysis						Multivariate analysis				
			Creatinine				Spearman's rank correlation						
	Level	n	Average	SE	95%CI		r	*P* value		Estimate	SE	*t* value	*P* value
Cariogenic bacteria	Much	994	0.75	0.01	0.73	– 0.76	0.053	<.05	Cariogenic bacteria	0.011	0.006	1.70	.089
	Average	495	0.72	0.01	0.70	– 0.74			Sex (woman/man)	−0.113	0.005	−21.62	<.01
	Little	399	0.72	0.01	0.69	– 0.74			Age (years)	0.002	0.000	4.17	<.01
						–			BMI (kg/m2)	0.004	0.002	2.84	<.01
						–			Smoking (no/yes)	−0.015	0.009	−1.64	.100
Acidity	Much	1239	0.71	0.01	0.69	– 0.72	−0.160	<.01	Acidity	−0.044	0.007	−6.09	<.01
	Average	430	0.74	0.01	0.72	– 0.76			Sex (woman/man)	−0.109	0.005	−20.90	<.01
	Little	219	0.85	0.02	0.82	– 0.88			Age (years)	0.002	0.000	4.02	<.01
						–			BMI (kg/m2)	0.005	0.002	3.05	<.01
						–			Smoking (no/yes)	−0.020	0.009	−2.17	.030
Buffer capacity	Much	757	0.78	0.01	0.76	– 0.80	0.209	<.01	Buffer capacity	0.020	0.007	3.01	<.01
	Average	640	0.71	0.01	0.69	– 0.73			Sex (woman/man)	−0.110	0.005	−20.79	<.01
	Little	491	0.68	0.01	0.66	– 0.70			Age (years)	0.001	0.000	3.27	<.01
						–			BMI (kg/m2)	0.004	0.002	2.82	<.01

(*continued*)

Table 7

(continued).

			Univariate analysis							Multivariate analysis				
			Creatinine					Spearman's rank correlation						
	Level	n	Average	SE	95%CI			r	*P* value		Estimate	SE	*t* value	*P* value
						–				Smoking (no/yes)	−0.016	0.009	−1.75	.081
Occult Blood	Much	940	0.75	0.01	0.73	–	0.76	0.080	<.01	Occult Blood	0.003	0.007	0.40	.692
	Average	597	0.72	0.01	0.70	–	0.74			Sex (woman/man)	−0.113	0.005	−21.59	<.01
	Little	351	0.71	0.01	0.68	–	0.73			Age (years)	0.002	0.000	4.19	<.01
						–				BMI (kg/m2)	0.004	0.002	2.84	<.01
						–				Smoking (no/yes)	−0.015	0.009	−1.63	.104
Protein	Much	1254	0.74	0.01	0.73	–	0.76	0.067	<.01	Protein	0.004	0.007	0.58	.564
	Average	395	0.72	0.01	0.69	–	0.74			Sex (woman/man)	−0.113	0.005	−21.59	<.01
	Little	239	0.70	0.02	0.67	–	0.73			Age (years)	0.002	0.000	3.94	<.01
						–				BMI (kg/m2)	0.004	0.002	2.87	<.01
						–				Smoking (no/yes)	−0.016	0.009	−1.66	.098
Leukocyte	Much	1050	0.73	0.01	0.71	–	0.74	0.001	.959	Leukocyte	−0.002	0.007	−0.30	.765
	Average	545	0.74	0.01	0.72	–	0.76			Sex (woman/man)	−0.113	0.005	−21.59	<.01
	Little	293	0.73	0.01	0.70	–	0.76			Age (years)	0.002	0.000	4.39	<.01
						–				BMI (kg/m2)	0.004	0.002	2.90	<.01
						–				Smoking (no/yes)	−0.015	0.009	−1.65	.099
Ammonia	Much	1539	0.74	0.01	0.73	–	0.75	0.114	<.01	**Ammonia**	0.013	0.010	1.30	.1954
	Average	255	0.69	0.02	0.66	–	0.72			Sex (woman/man)	−0.112	0.005	−21.45	<.01
	Little	94	0.66	0.03	0.61	–	0.71			Age (years)	0.002	0.000	3.90	<.01
						–				BMI (kg/m2)	0.004	0.002	2.84	<.01
										Smoking (no/yes)	−0.016	0.009	−1.67	.096

SE: standard error, CI: confidence interval.

Table 8

Correlation between the interval change of systolic blood pressure and that of salivary multi test in those who had no antihypertensive medication (n = 539).

			Univariate analysis						Multivariate analysis				
			Interval change of Systolic blood pressure					Tukey-Kramer HSD					
		n	Average	SE	95%CI			*P* value		Estimate	SE	*t* value	*P* value
Cariogenic bacteria	Remain high	136	1.169	1.079	−0.950	–	3.288	NS	Change in cariogenic bacteria	0.435	0.462	0.94	.347
	Increased	88	1.477	1.341	−1.157	–	4.112		Sex (woman/man)	0.168	0.549	0.31	.760
	Decreased	130	1.092	1.103	−1.075	–	3.260		age (2017)	0.029	0.044	0.65	.515
	Remain low	185	−0.524	0.925	−2.341	–	1.293		Change in BMI	0.868	0.358	2.42	<.05
						–			Change in smoking habit	1.264	0.803	1.57	.116
Acidity	Remain high	266	1.008	0.772	−0.509	–	2.524	NS	Change in acidity	0.321	0.475	0.68	.500
	Increased	99	0.748	1.265	−1.738	–	3.233		Sex (woman/man)	0.126	0.552	0.23	.819
	Decreased	76	−1.013	1.444	−3.850	–	1.824		age (2017)	0.041	0.044	0.93	.352
	Remain low	98	0.704	1.272	−1.794	–	3.203		Change in BMI	0.882	0.358	2.46	<.05
						–			Change in smoking habit	1.298	0.802	1.62	.106
Buffer capacity	Remain high	77	−0.558	1.435	−3.378	–	2.261	NS	Change in Buffer capacity	−0.433	0.499	−0.87	.385
	Increased	75	0.587	1.454	−2.270	–	3.444		Sex (woman/man)	0.214	0.551	0.39	.698
	Decreased	83	0.145	1.383	−2.571	–	2.860		age (2017)	0.026	0.045	0.59	.555
	Remain low	304	1.056	0.722	−0.363	–	2.475		Change in BMI	0.881	0.358	2.46	<.05
						–			Change in smoking habit	1.337	0.800	1.67	.095
Occult Blood	Remain high	168	0.881	0.968	−1.021	–	2.783	NS	Change in occult blood	0.551	0.431	1.28	.202
	Increased	108	2.787	1.208	0.415	–	5.159		Sex (woman/man)	0.175	0.548	0.32	.749
	Decreased	59	−0.458	1.634	−3.667	–	2.752		age (2017)	0.024	0.044	0.55	.583
	Remain low	204	−0.431	0.879	−2.157	–	1.295		Change in BMI	0.879	0.358	2.46	<.05
						–			Change in smoking habit	1.297	0.800	1.62	.106
Protein	Remain high	233	2.498	0.815	0.898	–	4.098	<.01	Change in protein	1.658	0.435	3.81	<.01
	Increased	65	2.092	1.542	−0.937	–	5.122		Sex (woman/man)	0.104	0.542	0.19	.848
	Decreased	74	−0.176	1.445	−3.015	–	2.663		age (2017)	−0.024	0.046	−0.52	.600
	Remain low	167	−2.222	0.962	−4.111	–	−0.332		Change in BMI	0.869	0.354	2.46	<.05
						–			Change in smoking habit	1.328	0.790	1.68	.093
Leukocyte	Remain high	194	2.083	0.897	0.320	–	3.845	<.05	Change in leukocyte	1.180	0.433	2.73	<.01
	Increased	93	1.538	1.296	−1.008	–	4.083		Sex (woman/man)	0.024	0.548	0.04	.965

(*continued*)

Table 8

(continued).

		Univariate analysis							Multivariate analysis				
		Interval change of Systolic blood pressure					Tukey-Kramer HSD						
		n	Average	SE	95%CI			P value		Estimate	SE	t value	P value
	Decreased	85	1.082	1.355	−1.580	–	3.745		age (2017)	0.017	0.044	0.39	.698
	Remain low	167	−1.826	0.967	−3.726	–	0.073		Change in BMI	0.869	0.356	2.44	<.05
						–			Change in smoking habit	1.224	0.796	1.54	.125
Ammonia	Remain high	362	0.950	0.662	−0.350	–	2.251	NS	Change in ammonia	0.501	0.549	0.91	.362
	Increased	57	−0.105	1.668	−3.382	–	3.172		Sex (woman/man)	0.228	0.553	0.41	.681
	Decreased	64	0.750	1.574	−2.342	–	3.842		age (2017)	0.023	0.046	0.51	.609
	Remain low	56	−0.929	1.683	−4.234	–	2.377		Change in BMI	0.881	0.358	2.46	<.05
									Change in smoking habit	1.387	0.802	1.73	.085

SE: standard error, CI: confidence interval, NS: not significant, HSD: honestly significant difference

Table 9

Correlation between the interval change of diastolic blood pressure and that of salivary multi test in those who had no antihypertensive medication (n = 539).

		Univariate analysis							Multivariate analysis				
		Interval change of diastolic blood pressure					Tukey-Kramer HSD						
		n	Average	SE	95%CI			P value		Estimate	SE	t value	P value
Cariogenic bacteria	Remain high	136	0.066	0.713	−1.334	–	1.466	NS	Change in cariogenic bacteria	0.444	0.304	1.46	.144
	Increased	88	−0.352	0.886	−2.092	–	1.388		Sex (woman/man)	0.612	0.361	1.70	.090
	Decreased	130	0.092	0.729	−1.339	–	1.524		age (2017)	0.002	0.029	0.08	.934
	Remain low	185	−1.616	0.611	−2.816	–	−0.416		Change in BMI	0.693	0.236	2.94	<.01
						–			Change in smoking habit	0.868	0.528	1.64	.101
Acidity	Remain high	266	−0.004	0.510	−1.006	–	0.998	NS	Change in acidity	0.244	0.313	0.78	.435
	Increased	99	−1.404	0.836	−3.047	–	0.239		Sex (woman/man)	0.580	0.364	1.60	.111
	Decreased	76	−1.526	0.954	−3.401	–	0.349		age (2017)	0.014	0.029	0.47	.637
	Remain low	98	−0.541	0.841	−2.192	–	1.110		Change in BMI	0.707	0.236	2.99	<.01
						–			Change in smoking habit	0.912	0.528	1.73	.085
Buffer capacity	Remain high	77	−1.844	0.949	−3.708	–	0.020	NS	Change in Buffer capacity	−0.272	0.328	−0.83	.408
	Increased	75	0.253	0.961	−1.635	–	2.142		Sex (woman/man)	0.641	0.363	1.77	.078
	Decreased	83	−0.241	0.914	−2.036	–	1.554		age (2017)	0.004	0.030	0.13	.900
	Remain low	304	−0.546	0.477	−1.484	–	0.392		Change in BMI	0.706	0.236	2.99	<.01
						–			Change in smoking habit	0.941	0.527	1.78	.075
Occult Blood	Remain high	168	−0.524	0.644	−1.788	–	0.741	NS	Change in occult blood	0.082	0.284	0.29	.772
	Increased	108	−0.269	0.803	−1.846	–	1.309		Sex (woman/man)	0.613	0.362	1.69	.091
	Decreased	59	−0.644	1.086	−2.778	–	1.490		age (2017)	0.008	0.029	0.27	.789
	Remain low	204	−0.755	0.584	−1.902	–	0.393		Change in BMI	0.705	0.236	2.99	<.01
						–			Change in smoking habit	0.933	0.528	1.77	.078
Protein	Remain high	233	0.142	0.542	−0.923	–	1.206	<.05	Change in protein	0.763	0.288	2.65	<.01
	Increased	65	0.092	1.026	−1.923	–	2.108		Sex (woman/man)	0.583	0.359	1.62	.106
	Decreased	74	0.311	0.962	−1.578	–	2.200		age (2017)	−0.018	0.030	−0.59	.555
	Remain low	167	−2.222	0.640	−3.479	–	−0.964		Change in BMI	0.700	0.235	2.98	<.01
						–			Change in smoking habit	0.936	0.524	1.79	.075
Leukocyte	Remain high	194	−0.278	0.599	−1.455	–	0.898	NS	Change in leukocyte	0.167	0.287	0.58	.561
	Increased	93	−0.366	0.865	−2.064	–	1.333		Sex (woman/man)	0.591	0.363	1.63	.104
	Decreased	85	−0.577	0.905	−2.353	–	1.200		age (2017)	0.007	0.029	0.24	.813
	Remain low	167	−1.030	0.645	−2.298	–	0.238		Change in BMI	0.703	0.236	2.98	<.01
						–			Change in smoking habit	0.923	0.528	1.75	.081
Ammonia	Remain high	362	−0.365	0.438	−1.225	–	0.496	NS	Change in ammonia	0.459	0.361	1.270	.205
	Increased	57	−0.842	1.104	−3.012	–	1.327		Sex (woman/man)	0.667	0.364	1.83	.067
	Decreased	64	−0.672	1.042	−2.719	–	1.375		age (2017)	−0.002	0.030	−0.06	.952
	Remain low	56	−1.536	1.114	−3.724	–	0.653		Change in BMI	0.706	0.236	2.99	<.01
									Change in smoking habit	0.987	0.528	1.87	.062

SE: standard error CI: confidence interval, NS: not significant HSD: honestly significant difference

The correlations between the interyear changes in the serum levels of triglycerides or HDL-C and the interyear changes in the saliva test results are shown in Tables 10 and 11. This analysis included the data for the subjects who were not taking antihyperlipidemic medication in either 2017 or 2018 (n = 608). A significant inverse correlation was found between the interyear change in the serum triglyceride level and the interyear change in the buffer capacity of saliva in the multivariate analysis ($P < .05$), even though no significant correlation between these parameters was detected in the univariate analysis.

Table 10

Correlation between the interval change of triglyceride and that of salivary multi test in those who had no antihyperlipidemic medication (n = 608).

	Univariate analysis								Multivariate analysis				
			Interval change of triglyceride					Tukey-Kramer HSD					
		n	Average	SE	95%CI			*P* value		Estimate	SE	*t* value	*P* value
Cariogenic bacteria	Remain high	157	3.02	4.50	−5.82	–	11.85	NS	Change in cariogenic bacteria	1.288	1.863	0.69	.490
	Increased	100	2.34	5.64	−8.73	–	13.41		Sex (woman/man)	−0.865	2.217	−0.39	.697
	Decreased	150	8.43	4.60	−0.61	–	17.47		age (2017)	−0.448	0.180	−2.49	<.05
	Remain low	201	−1.33	3.98	−9.14	–	6.47		Change in BMI	9.685	1.196	8.10	<.01
						–			Change in smoking habit	−4.117	3.333	−1.24	.217
Acidity	Remain high	300	3.24	3.26	−3.16	–	9.64	NS	Change in acidity	−0.490	1.900	−0.260	.797
	Increased	111	0.84	5.36	−9.69	–	11.36		Sex (woman/man)	−0.864	2.232	−0.39	.699
	Decreased	86	6.44	6.09	−5.51	–	18.40		age (2017)	−0.434	0.180	−2.41	<.05
	Remain low	111	0.77	5.36	−9.76	–	11.29		Change in BMI	9.719	1.195	8.13	<.01
						–			Change in smoking habit	−3.997	3.338	−1.20	.232
Buffer capacity	Remain high	85	−8.35	6.10	−20.34	–	3.63	NS	Change in Buffer capacity	−4.479	2.010	−2.23	<.05
	Increased	83	6.40	6.17	−5.73	–	18.52		Sex (woman/man)	−0.345	2.222	−0.16	.877
	Decreased	95	−0.73	5.77	−12.06	–	10.61		age (2017)	−0.516	0.181	−2.85	<.01
	Remain low	345	5.66	3.03	−0.29	–	11.61		Change in BMI	9.663	1.190	8.12	<.01
						–			Change in smoking habit	−3.932	3.320	−1.18	.237
Occult Blood	Remain high	214	1.21	3.84	−6.34	–	8.76	NS	Change in occult blood	−0.516	1.709	−0.30	.763
	Increased	106	−1.80	5.46	−12.53	–	8.93		Sex (woman/man)	−0.957	2.217	−0.43	.666
	Decreased	68	17.21	6.82	3.81	–	30.60		age (2017)	−0.416	0.181	−2.30	<.05
	Remain low	220	2.12	3.79	−5.32	–	9.57		Change in BMI	9.724	1.195	8.14	<.01
						–			Change in smoking habit	−4.026	3.333	−1.21	.228
Protein	Remain high	287	3.42	3.33	−3.12	–	9.96	NS	Change in protein	1.968	1.749	1.13	.261
	Increased	60	7.27	7.28	−7.03	–	21.56		Sex (woman/man)	−0.970	2.214	−0.44	.661
	Decreased	77	7.42	6.43	−5.21	–	20.04		age (2017)	−0.498	0.188	−2.64	<.01
	Remain low	184	−1.54	4.16	−9.70	–	6.63		Change in BMI	9.635	1.196	8.06	<.01
						–			Change in smoking habit	−4.070	3.330	−1.22	.222
Leukocyte	Remain high	228	4.04	3.73	−3.30	–	11.37	NS	Change in leukocyte	2.276	1.748	1.30	.193
	Increased	99	7.80	5.67	−3.33	–	18.93		Sex (woman/man)	−1.161	2.219	−0.52	.601
	Decreased	99	3.11	5.67	−8.02	–	14.24		age (2017)	−0.464	0.180	−2.59	<.05
	Remain low	182	−1.63	4.18	−9.84	–	6.58		Change in BMI	9.680	1.194	8.11	<.01
						–			Change in smoking habit	−4.324	3.335	−1.30	.195
Ammonia	Remain high	416	3.71	2.77	−1.72	–	9.15	NS	Change in ammonia	2.472	2.232	1.110	.269
	Increased	65	0.12	7.00	−13.63	–	13.88		Sex (woman/man)	−0.629	2.231	−0.28	.778
	Decreased	65	3.12	7.00	−10.63	–	16.88		age (2017)	−0.484	0.185	−2.62	<.01
	Remain low	62	−0.82	7.17	−14.90	–	13.26		Change in BMI	9.692	1.194	8.12	<.01
									Change in smoking habit	−3.714	3.343	−1.11	.267

SE: standard error CI: confidence interval, NS: not significant HSD: honestly significant difference

The correlations between the interyear change in the serum HbA1C level and the interyear changes in the saliva test results are shown in Table 12. This analysis included the data for the subjects who were not taking antidiabetic medication in either 2017 or 2018 (n = 728). The interyear change in the serum HbA1C level was shown to be significantly correlated with the interyear change in the salivary protein level in the univariate analyses ($P < .05$), and the correlation between these parameters was found to be nearly significant in the multivariate analysis ($P = .052$). Increased serum HbA1C levels were seen in the subjects who had high salivary protein levels in both 2017 and 2018, while decreased serum HbA1C levels were observed in those that displayed low salivary protein levels in both years.

The correlations between the interyear change in the serum creatinine level and the interyear changes in the saliva test results are shown in Table 13. No significant correlations were found between these parameters.

4. Discussion

Saliva is widely used for diagnostic purposes, monitoring systemic disease status, and predicting disease progression.[26] The purpose of this study was to investigate the associations between the results of saliva tests and MetS based on medical health check-up data for a large population.

Both the longitudinal and cross-sectional studies showed a significant relationship between salivary protein levels and serum HbA1c levels. The subjects with higher serum HbA1c levels had higher salivary protein levels. The SMT was used to measure three items (the salivary levels of occult blood and protein and the salivary WBC count) as markers of periodontal disease. In a study involving the SMT, periodontal pocket depth, bleeding on probing, and the Community Periodontal Index were reported to be correlated with salivary occult blood and protein levels as well as the salivary WBC count.[27] Salivary occult blood and protein levels and the salivary WBC count are considered to be markers of inflammation in periodontal tissue. Salivary protein

Table 11

Correlation between the interval change of HDL-cholesterol and that of salivary multi test in those who had no antihyperlipidemic medication (n = 608).

	Univariate analysis								Multivariate analysis				
		Interval change of HDL-cholesterol					Tukey-Kramer HSD						
		n	Average	SE	95%CI			*P* value		Estimate	SE	*t* value	*P* value
Cariogenic bacteria	Remain high	157	−0.09	0.89	−1.83	–	1.65	NS	Change in cariogenic bacteria	−0.290	0.358	−0.81	.418
	Increased	100	−0.62	1.11	−2.80	–	1.56		Sex (woman/man)	−0.749	0.426	−1.76	.079
	Decreased	150	−0.56	0.91	−2.34	–	1.22		age (2017)	0.006	0.035	0.18	.854
	Remain low	201	1.03	0.78	−0.51	–	2.57		Change in BMI	−2.283	0.230	−9.93	<.01
						–			Change in smoking habit	−0.296	0.641	−0.46	.645
Acidity	Remain high	300	0.36	0.64	−0.90	–	1.62	NS	Change in acidity	0.437	0.365	1.20	.232
	Increased	111	0.08	1.06	−1.99	–	2.16		Sex (woman/man)	−0.797	0.429	−1.86	.064
	Decreased	86	−0.33	1.20	−2.68	–	2.03		age (2017)	0.008	0.035	0.23	.822
	Remain low	111	−0.37	1.06	−2.45	–	1.71		Change in BMI	−2.292	0.230	−9.98	<.01
						–			Change in smoking habit	−0.354	0.641	−0.55	.581
Buffer capacity	Remain high	85	0.11	1.21	−2.27	–	2.48	NS	Change in Buffer capacity	0.131	0.388	0.34	.736
	Increased	83	0.10	1.22	−2.30	–	2.50		Sex (woman/man)	−0.751	0.429	−1.75	.081
	Decreased	95	0.56	1.14	−1.69	–	2.80		age (2017)	0.004	0.035	0.12	.907
	Remain low	345	−0.06	0.60	−1.24	–	1.11		Change in BMI	−2.288	0.230	−9.95	<.01
						–			Change in smoking habit	−0.316	0.641	−0.49	.623
Occult Blood	Remain high	214	0.49	0.76	−1.00	–	1.98	NS	Change in occult blood	0.059	0.329	0.18	.858
	Increased	106	−0.84	1.08	−2.96	–	1.28		Sex (woman/man)	−0.731	0.426	−1.71	.087
	Decreased	68	−0.51	1.35	−3.16	–	2.14		age (2017)	0.000	0.035	0.01	.994
	Remain low	220	0.30	0.75	−1.17	–	1.78		Change in BMI	−2.291	0.230	−9.96	<.01
						–			Change in smoking habit	−0.314	0.641	−0.49	.624
Protein	Remain high	287	−0.36	0.65	−1.64	–	0.93	NS	Change in protein	0.087	0.337	0.26	.797
	Increased	60	0.58	1.43	−2.23	–	3.40		Sex (woman/man)	−0.735	0.426	−1.73	.085
	Decreased	77	2.58	1.26	0.10	–	5.07		age (2017)	−0.002	0.036	−0.05	.963
	Remain low	184	−0.46	0.82	−2.06	–	1.15		Change in BMI	−2.294	0.230	−9.96	<.01
						–			Change in smoking habit	−0.314	0.641	−0.49	.625
Leukocyte	Remain high	228	0.00	0.74	−1.45	–	1.44	NS	Change in leukocyte	0.065	0.337	0.19	.847
	Increased	99	−0.45	1.12	−2.65	–	1.74		Sex (woman/man)	−0.740	0.427	−1.73	.084
	Decreased	99	0.90	1.12	−1.30	–	3.10		age (2017)	0.000	0.035	0.01	.992
	Remain low	182	0.03	0.83	−1.59	–	1.65		Change in BMI	−2.291	0.230	−9.96	<.01
						–			Change in smoking habit	−0.320	0.642	−0.50	.618
Ammonia	Remain high	416	−0.32	0.54	−1.39	–	0.75	NS	Change in ammonia	−0.260	0.430	−0.610	.545
	Increased	65	3.37	1.37	0.67	–	6.07		Sex (woman/man)	−0.766	0.429	−1.78	.075
	Decreased	65	−0.48	1.37	−3.18	–	2.22		age (2017)	0.008	0.036	0.21	.832
	Remain low	62	−0.11	1.41	−2.88	–	2.65		Change in BMI	−2.287	0.230	−9.95	<.01
									Change in smoking habit	−0.347	0.643	−0.54	.590

CI = confidence interval, HSD = honestly significant difference, NS = not significant, SE = standard error.

composition was also reported to be affected by the development of periodontitis.[28] In addition, many investigators have suggested that a two-way relationship exists between DM and periodontal disease.[29,30] Previously, it was reported that salivary protein concentration was higher in DM patients with HbA1c levels of >0.7% than in those with HbA1c levels of <0.7%.[31] It was also stated that the increase in the salivary protein concentration was due to a reduction in salivary secretion and inflammatory oral conditions, including periodontitis, in individuals with DM.[31] These results suggested that the protein content of saliva increases in DM patients because of periodontal disease and hyposalivation, and therefore, the salivary protein level could be a useful marker of both periodontal disease and hyperglycemia.

In this study, the longitudinal analysis revealed significant correlations between the interyear change in systolic blood pressure and the interyear changes in the salivary protein level and WBC count, and between the interyear change in diastolic blood pressure and the interyear change in the salivary protein level. In the cross-sectional analysis, significant relationships were observed between the salivary levels of protein or occult blood and blood pressure in the univariate analyses. These findings suggested that a causal relationship exists between higher salivary protein levels and increased blood pressure/hypertension. As stated above, the salivary protein level is a marker of periodontal disease. A few previous studies have investigated the associations among hypertension, blood pressure, and periodontal disease.[32–34] In a prospective Japanese cohort study conducted over three years, it was suggested that the progression of periodontal disease might be associated with blood pressure.[34] In another four-year longitudinal study involving Japanese employees, the worsening of hypertension was also reported to be correlated with the presence of periodontal pockets.[32] On the other hand, it was reported that there was no association between periodontal measurements and hypertension in a cohort study of middle-aged health-professionals.[33] Although the precise mechanism responsible for the association between hypertension and periodontal disease remains uncertain, increased levels of C-reactive protein,

Table 12

Correlation between the interval change of HbA1C and that of salivary multi test in those who had no antidiabetic medication (n = 728).

	Univariate analysis								Multivariate analysis				
			Interval change of HbA1C					Tukey-Kramer HSD					
		n	Average	SE	95%CI			*P* value		Estimate	SE	*t* value	*P* value
Cariogenic bacteria	Remain high	194	0.05	0.02	0.01	–	0.09	NS	Change in cariogenic bacteria	0.012	0.009	1.45	.147
	Increased	117	0.00	0.03	−0.05	–	0.05		Sex (woman/man)	−0.010	0.010	−0.99	.325
	Decreased	183	0.01	0.02	−0.03	–	0.05		age (2017)	0.001	0.001	1.48	.139
	Remain low	234	−0.01	0.02	−0.04	–	0.03		Change in BMI	0.039	0.005	7.36	<.01
						–			Change in smoking habit	−0.018	0.015	−1.14	.256
Acidity	Remain high	359	0.01	0.01	−0.02	–	0.04	NS	Change in acidity	0.000	0.009	−0.04	.968
	Increased	135	−0.01	0.02	−0.06	–	0.04		Sex (woman/man)	−0.011	0.010	−1.05	.295
	Decreased	95	0.05	0.03	−0.01	–	0.10		age (2017)	0.001	0.001	1.74	.082
	Remain low	139	0.02	0.02	−0.03	–	0.07		Change in BMI	0.039	0.005	7.38	<.01
						–			Change in smoking habit	−0.016	0.015	−1.03	.301
Buffer capacity	Remain high	91	−0.02	0.03	−0.08	–	0.03	NS	Change in Buffer capacity	−0.007	0.010	−0.74	.457
	Increased	102	0.03	0.03	−0.02	–	0.09		Sex (woman/man)	−0.010	0.010	−0.95	.341
	Decreased	114	−0.03	0.03	−0.08	–	0.02		age (2017)	0.001	0.001	1.54	.124
	Remain low	421	0.03	0.01	0.00	–	0.05		Change in BMI	0.039	0.005	7.37	<.01
						–			Change in smoking habit	−0.016	0.015	−1.05	.294
Occult Blood	Remain high	250	0.04	0.02	0.01	–	0.08	<.05	Change in occult blood	0.006	0.008	0.74	.457
	Increased	132	−0.04	0.02	−0.08	–	0.01		Sex (woman/man)	−0.010	0.010	−1.03	.305
	Decreased	79	0.03	0.03	−0.03	–	0.09		age (2017)	0.001	0.001	1.61	.108
	Remain low	267	0.00	0.02	−0.03	–	0.04		Change in BMI	0.039	0.005	7.37	<.01
						–			Change in smoking habit	−0.017	0.015	−1.07	.284
Protein	Remain high	346	0.04	0.01	0.01	–	0.07	<.05	Change in protein	0.016	0.008	1.95	.052
	Increased	74	0.00	0.03	−0.07	–	0.06		Sex (woman/man)	−0.011	0.010	−1.06	.291
	Decreased	98	0.03	0.03	−0.03	–	0.08		age (2017)	0.001	0.001	1.03	.303
	Remain low	210	−0.03	0.02	−0.07	–	0.01		Change in BMI	0.039	0.005	7.36	<.01
						–			Change in smoking habit	−0.017	0.015	−1.07	.284
Leukocyte	Remain high	273	0.03	0.02	0.00	–	0.07	NS	Change in leukocyte	0.013	0.008	1.65	.098
	Increased	124	0.02	0.03	−0.03	–	0.07		Sex (woman/man)	−0.012	0.010	−1.22	.224
	Decreased	119	0.00	0.03	−0.05	–	0.05		age (2017)	0.001	0.001	1.50	.135
	Remain low	212	−0.01	0.02	−0.05	–	0.03		Change in BMI	0.039	0.005	7.37	<.01
						–			Change in smoking habit	−0.018	0.015	−1.15	.251
Ammonia	Remain high	497	0.03	0.01	0.01	–	0.06	NS	Change in ammonia	0.016	0.010	1.580	.116
	Increased	80	−0.05	0.03	−0.11	–	0.02		Sex (woman/man)	−0.009	0.010	−0.86	.389
	Decreased	83	−0.03	0.03	−0.09	–	0.03		age (2017)	0.001	0.001	1.29	.196
	Remain low	68	−0.01	0.03	−0.07	–	0.06		Change in BMI	0.039	0.005	7.39	<.01
									Change in smoking habit	−0.015	0.015	−0.96	.340

CI = confidence interval, HSD = honestly significant difference, NS = not significant, SE = standard error.

which are seen in patients with hypertension, coronary arterial heart disease, and periodontal disease, might contribute to it.[18,35–38] In a randomized controlled trial, the intensive periodontal treatment group exhibited lower diastolic and systolic blood pressure and markedly smaller endothelial microparticles than the control group, as well as parallel improvements in periodontal status.[39] These findings suggested that there might be a relationship between periodontal disease and hypertension. Furthermore, the salivary protein level, which reflects periodontal tissue inflammation, could be a useful marker of both periodontal disease and hypertension. In addition to the salivary protein level, the salivary occult blood level and WBC count are also markers of periodontal tissue inflammation. The results of this study suggested that the salivary protein level displayed a stronger relationship with periodontal inflammation than the salivary occult blood level or WBC count. The critical reason why the salivary protein level exhibited the strongest relationship with periodontal inflammation was unclear although the measurement methods and the detection range of the test kit employed in this study (the SMT) might have contributed to it.

A significant relationship was also observed between salivary buffer capacity and the serum triglyceride level in both the cross-sectional and longitudinal analyses. The buffer capacity of saliva was lower in the subjects with higher levels of triglycerides/hyperlipidemia. Tremblay et al. investigated the association between salivary pH and MetS in females and reported that mean salivary pH levels decreased as the number of MetS components increased and that salivary pH was correlated with markers of MetS components, such as triglyceride levels.[40] Our results were consistent with the latter report. Salivary cholesterol concentrations were reported to reflect serum cholesterol concentrations to some extent.[41] The buffer capacity and pH of saliva are important and are affected by enzymes and the levels of bicarbonate, urea, and amphoteric proteins.[42,43] In particular, bicarbonate affects the buffering system, and the pH of saliva is dependent on the bicarbonate concentration. The salivary bicarbonate concentration decreases with the salivary flow rate, resulting in a reduction in the pH of saliva.[44] In hyperlipidemic patients with xerostomia, there a close relationship was detected between salivary gland swelling, salivary gland hypofunction,

Table 13

Correlation between the interval change of creatinine and that of salivary multi test (n = 781).

	Univariate analysis								Multivariate analysis				
			Interval change of creatinine					Tukey-Kramer HSD					
		n	Average	SE	95%CI			*P* value		Estimate	SE	*t* value	*P* value
Cariogenic bacteria	Remain high	207	0.002	0.008	−0.013		0.017	NS	Change in cariogenic bacteria	−0.006	0.003	−1.80	.073
	Increased	127	0.013	0.010	−0.006		0.033		Sex (woman/man)	0.009	0.004	2.33	<.05
	Decreased	195	0.023	0.008	0.007	–	0.039		age (2017)	0.000	0.000	0.38	.704
	Remain low	252	0.020	0.007	0.006	–	0.034		Change in BMI	0.017	0.002	8.64	<.01
						–			Change in smoking habit	−0.004	0.006	−0.62	.534
Acidity	Remain high	389	0.013	0.006	0.002	–	0.024	NS	Change in acidity	−0.002	0.003	−0.73	.468
	Increased	141	0.013	0.009	−0.005		0.032		Sex (woman/man)	0.010	0.004	2.46	<.05
	Decreased	103	0.017	0.011	−0.004		0.039		age (2017)	0.000	0.000	−0.04	.965
	Remain low	148	0.020	0.009	0.002	–	0.038		Change in BMI	0.017	0.002	8.59	<.01
						–			Change in smoking habit	−0.004	0.006	−0.67	.504
Buffer capacity	Remain high	95	0.015	0.011	−0.008		0.037	NS	Change in Buffer capacity	−0.003	0.004	−0.78	.437
	Increased	104	0.003	0.011	−0.018		0.025		Sex (woman/man)	0.010	0.004	2.48	<.05
	Decreased	121	0.019	0.010	−0.001	–	0.039		age (2017)	0.000	0.000	−0.13	.895
	Remain low	461	0.017	0.005	0.006	–	0.027		Change in BMI	0.017	0.002	8.58	<.01
						–			Change in smoking habit	−0.004	0.006	−0.74	.457
Occult Blood	Remain high	277	0.019	0.007	0.006	–	0.032	NS	Change in occult blood	0.001	0.003	0.42	.674
	Increased	139	0.001	0.009	−0.018		0.019		Sex (woman/man)	0.009	0.004	2.41	<.05
	Decreased	82	0.029	0.012	0.004	–	0.053		age (2017)	0.000	0.000	−0.02	.984
	Remain low	283	0.014	0.007	0.001	–	0.027		Change in BMI	0.017	0.002	8.61	<.01
						–			Change in smoking habit	−0.004	0.006	−0.73	.463
Protein	Remain high	382	0.017	0.006	0.006	–	0.029	NS	Change in protein	0.001	0.003	0.27	.784
	Increased	79	−0.005	0.013	−0.029		0.020		Sex (woman/man)	0.009	0.004	2.40	<.05
	Decreased	102	0.025	0.011	0.004	–	0.047		age (2017)	0.000	0.000	−0.04	.971
	Remain low	218	0.013	0.008	−0.002	–	0.027		Change in BMI	0.017	0.002	8.61	<.01
						–			Change in smoking habit	−0.004	0.006	−0.73	.466
Leukocyte	Remain high	294	0.009	0.007	−0.004		0.022	NS	Change in leukocyte	−0.005	0.003	−1.60	.110
	Increased	129	0.007	0.010	−0.012		0.026		Sex (woman/man)	0.010	0.004	2.56	<.05
	Decreased	132	0.029	0.010	0.010	–	0.048		age (2017)	0.000	0.000	0.30	.763
	Remain low	226	0.019	0.007	0.004	–	0.033		Change in BMI	0.017	0.002	8.59	<.01
						–			Change in smoking habit	−0.004	0.006	−0.66	.511
Ammonia	Remain high	543	0.016	0.005	0.007	–	0.026	NS	Change in ammonia	0.003	0.004	0.77	.441
	Increased	83	0.008	0.012	−0.016		0.033		Sex (woman/man)	0.010	0.004	2.47	<.05
	Decreased	87	0.023	0.012	−0.001	–	0.047		age (2017)	0.000	0.000	−0.16	.876
	Remain low	68	0.002	0.014	−0.025	–	0.028		Change in BMI	0.017	0.002	8.60	<.01
									Change in smoking habit	−0.004	0.006	−0.68	.495

CI = confidence interval, HSD = honestly significant difference, NS = not significant, SE = standard error.

and serum lipid levels.[45] These results indicate that associations exist between serum triglyceride levels and the salivary flow rate/salivary pH.

In the present study, the cross-sectional analysis (multivariate analysis) revealed a significant relationship between the serum creatinine level and the pH or buffer capacity of saliva. Both salivary pH and salivary buffer capacity were higher in the subjects with higher serum creatinine levels/decreased renal function. Previous studies have assessed salivary flow, pH, and buffer capacity in chronic kidney disease (CKD) patients. In one study, the CKD patients exhibited hyposalivation and increased salivary pH and buffer capacity.[46] Our results were consistent with the latter study. In CKD patients, the blood tends to become acidic (due to metabolic acidosis) as renal function degrades, and metabolic acidosis is a common finding.[47] Therefore, we speculated that the salivary pH might decrease as the serum creatinine level increases. However, our results showed the opposite, as was demonstrated in previous studies. A significant association between salivary and serum urea levels was reported to exist in pre-dialysis patients.[48] The hydrolysis of nitrogen compounds by bacterial urease has been reported to result in the production of carbon dioxide and ammonium ions, leading to increased alkalizing potential.[49] Impaired renal function might also affect salivary flow and salivary properties, which can result in saliva becoming alkaline.

The present study, which was based on health check-up data for a large population, is the first to demonstrate the utility of saliva tests for screening individuals for MetS/MetS components as well as periodontal disease. However, it had some limitations. For example, we used a commercially available saliva test kit. The test kit had a limited analytical ability and limited ranges of detection for salivary components. Another limitation was the cut-off values used for each test item in the SMT. In the SMT, the salivary WBC count and the salivary levels of occult blood, protein, and ammonia were classified into three grades. Further studies involving more sophisticated methods are required.[50]

In conclusion, correlations between the results of saliva tests and the results of health check-ups for MetS were revealed in a large population study. A longitudinal study revealed significant correlations between salivary protein levels and serum HbA1c

levels or blood pressure. In addition, a significant correlation was detected between the buffer capacity of saliva and the serum triglyceride level. Salivary pH increased irreversibly in subjects with impaired renal function. Therefore, saliva tests might be a useful tool for screening for not only periodontal disease but also MetS/MetS components in health check-ups of large populations.

Author contributions

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